REMARKS

RESTRICTION REQUIREMENT

Due to the restriction requirement, Applicants have canceled nonelected claims 10-11, 14-15, 23, 30-33 and 35-59 without prejudice to filing a continuing application directed thereto. Due to the cancellation of the claims, a request to delete inventors Presta and Adams is filed herewith.

AMENDMENTS

Typographical errors in the specification with respect to cited references are corrected herein.

To allay the Examiner's concerns about therapy of cancer where ErbB2 is not expressed, claim 1 has been amended to state that the "cancer expresses epidermal growth factor receptor (EGFR) and ErbB2," claim 27 states that the "cancer expresses but does not overexpress ErbB2 receptor," and claim 34 recites "colon, rectal and colorectal cancer which express ErbB2." Support for these amendments can be found on page 16, lines 32-34, for instance, which refers to cancer which produces sufficient levels of ErbB2 at the surface of cells thereof, such that an anti-ErbB2 antibody can bind thereto and have a therapeutic effect with respect to the cancer. The amendment is responsive to the 112, 1st paragraph rejection (basis C, see below), but Applicants believe that the amendment is non-limiting in that the originally presented claims encompassed successful therapy in any event.

To obviate 102 and 103 rejections, claim 3 has been incorporated into claim 1 and thus is canceled as moot. Hence, claim 1 encompasses therapy with antibodies including monoclonal antibody 2C4, rhuMAb 2C4 and other antibodies such as 7F3 which block binding of monoclonal antibody 2C4 to ErbB2 (page 50, line 28). Applicants specifically preserve the right to pursue original claim 1 in a continuing application.

Claims 60-62 have been added, with basis for these claims being found *at least* as follows:

claim 60 - claims 1 and 7
claim 61 - claims 1 and 16
claim 62 - claims 1 and 17

In that the amendments do not introduce new matter, entry thereof is respectfully requested.

SPECIFICATION

The Examiner states with respect to the trademark HERCEPTIN® that it should be capitalized wherever it appears and be accompanied by the generic terminology.

Applicants respond that the HERCEPTIN® trademark is capitalized throughout the specification and, where it first appears in the specification (page 2, lines 23-24), it is accompanied by the generic terminology (huMAb4D5-8 or rhuMAb HER2). Clearly the specification protects the proprietary nature of the HERCEPTIN® trademark.

Reconsideration of the objection is requested.

INFORMATION DISCLOSURE STATEMENT

The Examiner identifies missing IDS references on page 3 of the Office Action. Applicants hand delivered the missing references to the PTO on June 11, 2002. Consideration of all the cited art and return of the initialed PTO-1449 forms is respectfully requested.

SECTION 112, FIRST PARAGRAPH

Claims 1-8, 12-13, 16-21 and 24-27 are rejected under 35 USC Section 112, first paragraph on the basis that the specification while being enabling for a method of treating breast, lung or prostate cancer in xenograft models, wherein the cancer overexpresses ErbB2, using the anti-ErbB2 antibody 2C4, 7C2 or 4D5, does not reasonably provide enablement for treating any human having any cancer which expresses EGFR using any antibody which binds ErbB2.

The Examiner's bases for the rejection are:

A. The specification has not demonstrated the reproducible production of antibodies which have properties like 2C4 or HERCEPTIN®.

B. The claims encompass the experimental and unpredictable field of *in vivo* therapy for cancer in humans.

C. The claims do not recite that the cancer which is being treated need express ErbB2 at all.

These bases of the rejection are each addressed below.

A. The Examiner urges with regard to the broadly claimed "antibody which binds ErbB2" that the specification has not demonstrated the reproducible production of antibodies which have properties identical to 2C4 or Herceptin® nor of antibodies of other species origin which have the claimed properties. The Examiner relies on Xu *et al. International Journal of Cancer* 53(3):401-408(1993) (hereinafter "Xu *et al.*") and Shepard *et al. J. Clin. Immunol.* 11(3):117-127 (1991) (hereinafter "Shepard *et al.*") as establishing that "antibodies to the ErbB2 receptor exhibit highly variant activity."

Applicants submit that the specification enables the presently claimed invention. The claims herein refer to therapy with an antibody which binds ErbB2 and blocks binding of monoclonal antibody 2C4 to ErbB2 and/or which blocks ligand activation of an ErbB receptor. The specification provides clear guidance as to how to make an antibody which binds to ErbB2 (pages 21-31, for instance) and further how to screen for antibodies which block binding of monoclonal antibody 2C4 to ErbB2 (page 13, lines 35-36; page 15, lines 20-25; page 34, lines 13-15; and Example 1); or how to screen for antibodies which block ligand activation of an ErbB receptor (page 13, lines 16-28; page 31, lines 38 through to line 10 on page 33; and the Examples). Moreover, the specification enables representative species of the presently claimed genus of antibodies, specifically, monoclonal antibody 2C4, humanized 2C4, monoclonal antibody 7F3, humanized 7F3, L26, L96 and L288 (page 13, lines 24-28). Hence, Applicants submit that the present specification enables the methods

claimed herein involving an antibody that binds ErbB2 and blocks binding of monoclonal antibody 2C4 to ErbB2 and/or which blocks ligand activation of an ErbB receptor. Reconsideration of this basis of the rejection is respectfully requested.

B. The Examiner argues that the claims encompass the "experimental and unpredictable field of *in vivo* therapy for cancer in humans" and cites to Dillman *et al. Journal of Clinical Oncology* 12(7):1497-1515 (Jul 1994) (hereinafter "Dillman *et al.*") and Dermer *et al. Biotechnology* 12:320 (1994) (hereinafter "Dermer *et al.*") for stating, respectively, that "On the negative side is the observation that clinical results do not necessarily improve when humanized chimeric antibodies are used in humans, despite encouraging in vitro results in CDC and/or ADCC" and "What is significant in culture, for example immunotherapy's killing power or the transformation of 3T3 cells by a mutated proto-oncogene, simply does not have the same significance for cells *in vivo*."

Applicants submit that the presently claimed *in vivo* methods claimed herein are enabled by the specification. The present specification provides extensive guidance as to therapeutic administration of the antibodies (pages 43-47, for example), including working examples demonstrating *in vivo* therapy. For instance, Example 5 (page 58) shows that 2C4 significantly inhibited the growth of lung tumor cells *in vivo* (Fig. 11); Example 6 (page 58) explains that 2C4 will also suppress the growth of colorectal tumors *in vivo*; Example 7 (page 59) demonstrates that rhuMAb 2C4 was effective in inhibiting breast cancer tumor growth *in vivo*, where the breast cancer expressed but did not overexpress ErbB2 (Fig. 13); Examples 9-13 provide detailed guidance concerning human clinical trials with rhuMAb 2C4. Clearly, the present specification enables the presently claimed *in vivo* methods.

Turning now to the Examiner's reliance on Dillman *et al.* and Dermer *et al.*, Applicants submit that these references fail to demonstrate that the presently claimed invention is not enabled. Indeed, Dr. Dillman notes

that even in 1994 when his review article was published that it was "encouraging that tumor responses following monoclonal antibody therapy have been reported for both hematologic malignancies and solid tumor cancers." (Column 2, 3rd paragraph on page 1506 of Dillman *et al.*). In any event, these articles published in 1994 do not reflect the state of the art in 1999 when the present application was filed. While in 1994 there were no monoclonal antibodies approved by the FDA for human therapy, currently there are at least nine therapeutic monoclonal antibodies on the US market. Included within this list are several anti-cancer antibodies. For instance, in 1997, Genentech, the assignee of the present application, in collaboration with IDEC Pharmaceuticals achieved approval to market RITUXAN® (Rituximab), the first chimeric antibody approved for cancer therapy (non-Hodgkin's lymphoma). With the approval of HERCEPTIN® in 1998, Genentech became the first company to market a humanized antibody for metastatic breast cancer. Currently, there are at least 200 humanized therapeutic antibodies in various stages of clinical development, several for cancer therapy, including rhuMAb 2C4 the exemplified antibody of the present application. Clearly, those skilled in the oncology art would consider the invention herein to be enabled by the specification. Reconsideration and withdrawal of this basis of the rejection is respectfully requested.

C. The Examiner contends that the claims do not recite that the cancer which is being treated need express ErbB2 at all and states that there is "no guidance or objective evidence that an antibody which binds ErbB2 would have any effect at all on a cell which does not express the ErbB2 receptor."

This basis of the rejection is moot in view of the amendment of claim 1 to recite that the cancer expresses ErbB2, and the amendment of claim 27 to state that the cancer expresses but does not overexpress ErbB2. Applicants request reconsideration of this basis of the rejection.

Reconsideration and withdrawal of the Section 112, 1st paragraph rejection is respectfully requested in view of the above.

DEPOSIT

Claims 3 and 16-17 are rejected under 35 USC Section 112, first paragraph with respect to the 2C4 deposit.

The Examiner has suggested that a declaration be submitted as a means of completing the record. The requested declaration executed by the undersigned is submitted herewith.

Reconsideration of the rejection in view of the attached declaration is respectfully requested.

SECTION 102 - GREENE *ET AL.*

Claims 1-2, 4-6, 12 and 20 are rejected under 35 USC Section 102(e) as being anticipated by US Patent No. 5,824,311 (hereinafter "Greene *et al.*") as evidenced by Jardines *et al. Pathobiology* 61(5-6):268-282 (1993) (hereinafter "Jardines *et al.*") or Earp *et al. Breast Cancer Res and Treatment* 35:115-132 (1995) (hereinafter "Earp *et al.*").

This rejection is moot in view of the incorporation of non-rejected claim 3 into claim 1. Reconsideration and withdrawal of the rejection is respectfully requested.

SECTION 102 - ARAKAWA *ET AL.* OR HUDZIAK *ET AL.*

Claims 1-2, 4-6 and 20 are rejected under 35 USC Section 102(e) as being anticipated by US Patent No. 5,783,186 (hereinafter "Arakawa *et al.*") or US Patent No. 5,725,856 (hereinafter "Hudziak *et al.*") as evidenced by Jardines *et al.* or Earp *et al.*

This rejection is moot in view of the incorporation of non-rejected claim 3 into claim 1. Reconsideration and withdrawal of the rejection is respectfully requested.

SECTION 103 - GRIM *ET AL.* OR KERN *ET AL.*

Claims 1-2, 4-6, 12-13, 18, 20-21 and 24-26 are rejected under 35 USC

Section 103(a) as being unpatentable over Grim *et al. American Journal of Respiratory Cell & Molecular Biology* 15(3):348-354 (1996) (hereinafter "Grim *et al.*") or Kern *et al. American Journal of Respiratory Cell & Molecular Biology* 9(4):448-454 (1993) (hereinafter "Kern *et al.*") as evidenced by Jardines *et al.* or Earp *et al.* in view of Baselga *et al. Oncology* (Supplement No. 2) 11(3):43-48 (1997) (hereinafter "Baselga I") or Baselga *et al. J. Clin. Oncol.* 14(3):737-744 (1996) (hereinafter "Baselga II").

This rejection is moot in view of the incorporation of non-rejected claim 3 in claim 1. Reconsideration and withdrawal of the rejection is respectfully requested.

SECTION 103 - ARAKAWA *ET AL.* OR HUDZIAK *ET AL.*

Claims 1-2, 4-6, 12-13, 18 and 20-21 are rejected under 35 USC Section 103(a) as being unpatentable over Arakawa *et al.* or Hudziak *et al.* as evidenced by Jardines *et al.* or Earp *et al.* in view of Grim *et al.* or Kern *et al.*

This rejection is moot in view of the incorporation of non-rejected claim 3 in claim 1. Reconsideration and withdrawal of the rejection is respectfully requested.

SECTION 103 - GREENE *ET AL.* OR ARAKAWA *ET AL.* OR HUDZIAK *ET AL.*

Claims 1-7, 12-13, 16-18, 20-21 and 24-26 are rejected under 35 USC Section 103(a) as being unpatentable over Greene *et al.* or Arakawa *et al.* or Hudziak *et al.* as evidenced by Jardines *et al.* or Earp *et al.* and Grim *et al.* or Kern *et al.* and Baselga I or Baselga II in view of Fendly *et al. Cancer Research* 50:1550-1558 (1990) (hereinafter "Fendly *et al.*") or Shepard *et al. J. Clin. Immunol.* 11(3):117-127 (1991) (hereinafter "Shepard *et al.*"). Claims 1-7, 12-13, 16-21 and 24-26 are rejected under 35 USC Section 103(a) as being unpatentable over Greene *et al.* or Arakawa *et al.* or Hudziak *et al.* as evidenced by Jardines *et al.* or Earp *et al.* and Grim *et al.* or Kern *et al.* and Baselga I or Baselga II in view of

Fendly *et al.* or Shepard *et al.*, all in view of Schlom *Molecular Foundations of Oncology*, Broder, S. ed., Baltimore, MD:Williams & Wilkins, Chapter 6, pps. 95-134 (1991) (hereinafter "Schlom").

The primary references (Greene *et al.*, Arakawa *et al.*, Hudziak *et al.*, Jardines *et al.*, Earp *et al.*, Grim *et al.*, Kern *et al.*, Baselga I and Baselga II) are said to "fail to teach an antibody which blocks binding of 2C4 or the specific monoclonal antibody 2C4, or an antibody which blocks TGF-alpha activation of MAPK." Fendly *et al.* is relied on for teaching the monoclonal antibody 2C4, and that the antibody selectively binds ErbB2 (p. 1552). Shepard *et al.* is relied upon as teaching the monoclonal antibody 2C4, that the antibody selectively binds ErbB2 and is capable of treating ErbB2 positive cell lines (p. 123 is cited). The Examiner urges that blocking TGF-alpha activation of MAPK would be an inherent characteristic of the 2C4 antibody in Fendly *et al.* or Shepard *et al.* The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the 2C4 antibodies of Fendly *et al.* and Shepard *et al.* in the methods of the primary references, that one would have been motivated to do so because these antibodies selectively bind to ErbB2 and are able to treat cells which overexpress ErbB2, as taught by Fendly *et al.* and Shepard *et al.*

Applicants submit that the invention herein is patentable over the cited art. Claim 1 herein pertains to therapy of an EGFR-expressing cancer in a human comprising administering an antibody which binds ErbB2 and blocks binding of monoclonal antibody 2C4 to ErbB2. While the Examiner relies on Fendly *et al.* or Shepard *et al.* as providing motivation to use the 2C4 antibody in the methods of the primary references, Applicants submit that these two references would not have motivated the reader thereof to use the 2C4 for therapy as claimed herein, and actually would have taught away from such therapy.

Fendly *et al.* refers to 10 anti-HER2 antibodies, including 2C4 (see,

e.g., abstract). However, Fendly *et al.* does not suggest selection of the 2C4 antibody from the group of antibodies described for use in human therapy, let alone for therapy of a cancer which expresses EGFR as claimed herein.

Shepard *et al.*, published a year later, further characterizes the biological characteristics of the same panel of 10 anti-HER2 antibodies. However, based on the data presented in his paper, Shepard concludes: muMAb 4D5 was "clearly the most effective of the group" with respect to SK-BR3 human breast adenocarcinoma cell line which greatly overexpress $p185^{HER2}$ (paragraph bridging pages 119-120); that HER2 overexpression dependent-growth inhibition was a property shared by the monoclonal antibodies 4D5 and 3H4, whereas the other monoclonal antibodies varied in their ability to inhibit proliferation (column 1 on page 120); and that muMAb 4D5 was also clearly the most active with respect to its ability to inhibit the growth of SKOV-3, a human adenocarcinoma cell line that overexpresses $p185^{HER2}$ (column 2 on page 120). Shepard *et al.* concludes that the results show that when the monoclonal antibodies are compared for efficacy, muMAb 4D5 is usually the most potent and is therefore a good candidate for further characterization in other models (column 1 on page 121). Indeed, muMAb 4D5 was selected from the panel of 10 antibodies for development and, once humanized, became HERCEPTIN® which was approved for therapy of HER2 overexpressing metastatic breast cancer in 1998. Hence, Applicants submit that Shepard *et al.* teaches that muMAb 4D5 (which fails to block binding of monoclonal antibody 2C4 to ErbB2; see Table I on page 122 of Shepard *et al.*) should be used for therapy, as opposed to an antibody like 2C4 or rhuMAb 2C4 which blocks binding of monoclonal antibody 2C4 to ErbB2.

Indeed, Applicants submit that Shepard *et al.* <u>teaches away</u> from the use of 2C4 for therapy. In column 2 on page 120 of his paper Shepard notes that the potent growth inhibitory activity of 2C4 for MDA-MB-175 breast tumor cells is "not understood at present but may represent cross-reactivity with another receptor expressed on these cells." Shepard earlier explains that a critical property of an anti-$p185^{HER2}$ monoclonal

antibody with potential for therapy would be its lack of cross-reactivity with another receptor (column 2 on page 119). Hence, Applicants submit that Shepard *et al.* would have taught away from the use of the 2C4 antibody for therapy due to its potential cross-reactivity with another receptor.

Hence, Applicants submit that claims 1-7, 12-13, 16-18, 20-21 and 24-26 are patentable over the cited art.

Schlom is relied on as teaching the "various known antibody modifications, including FAb's and that they provide the therapeutic advantage of reducing the host anti-MAb response." Applicants submit that Schlom fails to describe or suggest therapy of EGFR expressing cancer with an antibody which binds ErbB2 and blocks binding of monoclonal antibody 2C4 to ErbB2. Hence, Applicants submit that claim 1 and its dependent claims are patentable over Schlom. Reconsideration and withdrawal of the rejection of claims 1-7, 12-13, 16-21 and 24-26 is respectfully requested.

Reconsideration and withdrawal of the Section 103 rejections is respectfully requested in view of the above.

Respectfully submitted,
GENENTECH, INC.

Date: August 1, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please replace the paragraph starting on page 1, line 27 with the following:

The second member of the ErbB family, p185^{neu}, was originally identified as the product of the transforming gene from neuroblastomas of chemically treated rats. The activated form of the *neu* proto-oncogene results from a point mutation (valine to glutamic acid) in the transmembrane region of the encoded protein. Amplification of the human homolog of *neu* is observed in breast and ovarian cancers and correlates with a poor prognosis (Slamon *et al.*, *Science*, 235:177-182 (1987); Slamon *et al.*, *Science*, 244:707-712 (1989); and US Pat No. 4,968,603). To date, no point mutation analogous to that in the *neu* proto-oncogene has been reported for human tumors. Overexpression of ErbB2 (frequently but not uniformly due to gene amplification) has also been observed in other carcinomas including carcinomas of the stomach, endometrium, salivary gland, lung, kidney, colon, thyroid, pancreas and bladder. See, among others, King *et al.*, *Science*, 229:974 (1985); Yokota *et al.*, *Lancet*: 1:765-767 (1986); [Fukushigi] Fukushige *et al.*, *Mol Cell Biol.*, 6:955-958 (1986); [Geurin] Guerin *et al.*, *Oncogene Res.*, 3:21-31 (1988); Cohen *et al.*, *Oncogene*, 4:81-88 (1989); Yonemura *et al.*, *Cancer Res.*, 51:1034 (1991); Borst *et al.*, *Gynecol. Oncol.*, 38:364 (1990); Weiner *et al.*, *Cancer Res.*, 50:421-425 (1990); Kern *et al.*, *Cancer Res.*, 50:5184 (1990); Park *et al.*, *Cancer Res.*, 49:6605 (1989); Zhau *et al.*, *Mol. Carcinog.*, 3:[354-357] 254-257 (1990); Aasland *et al. Br. J. Cancer* 57:358-363 (1988); Williams *et al. [Pathiobiology] Pathobiology* 59:46-52 (1991); and McCann *et al.*, *Cancer*, 65:88-92 (1990). ErbB2 may be overexpressed in prostate cancer (Gu *et al. Cancer Lett.* 99:185-9 (1996); Ross *et al. Hum. Pathol.* 28:827-33 (1997); Ross *et al. Cancer* 79:2162-70 (1997); and Sadasivan *et al. J. Urol.* 150:126-31 (1993)).

IN THE CLAIMS:

Please amend the pending claims as indicated below.

1. (Amended) A method of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2, comprising administering to the human a therapeutically effective amount of an antibody which binds ErbB2 and blocks binding of monoclonal antibody 2C4 to ErbB2.

Please cancel claim 3 without prejudice or disclaimer.
Please cancel claims 10-11 without prejudice or disclaimer.
Please cancel claims 14-15 without prejudice or disclaimer.
Please cancel claim 23 without prejudice or disclaimer.

27. (Amended) A method of treating cancer in a human, wherein the cancer [is not characterized by overexpression of the] expresses but does not overexpress ErbB2 receptor, comprising administering to the human a therapeutically effective amount of an antibody which binds to ErbB2 and blocks ligand activation of an ErbB receptor.

Please cancel claims 30-33, without prejudice or disclaimer.

34. (Amended) A method of treating cancer in a human, wherein the cancer is selected from the group consisting of colon, rectal and colorectal cancer which express ErbB2, comprising administering to the human a therapeutically effective amount of an antibody which binds ErbB2 and blocks ligand activation of an ErbB receptor.

Please cancel claims 35-59 without prejudice or disclaimer.

Please add the following claims:

60. (New) A method of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2, comprising

administering to the human a therapeutically effective amount of an antibody which binds ErbB2 and blocks TGF-α activation of mitogen-activated protein kinase (MAPK).

61. (New) A method of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2, comprising administering to the human a therapeutically effective amount of an antibody which has a biological characteristic of monoclonal antibody 2C4.

62. (New) A method of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2, comprising administering to the human a therapeutically effective amount of monoclonal antibody 2C4 or humanized 2C4.